Corticotropin releasing factor

Corticotropin releasing factor receptor antagonists: potential future therapy in gastroenterology?

Y Taché

New corticotropin releasing factor (CRF) antagonists in irritable bowel disease (IBS) warrant testing, and CRF_1 receptors may be a promising target for the treatment of IBS

Recent years have witnessed important developments in the understanding of the biochemical coding of stress.[1] In addition to the 41 amino acid peptide, corticotropin releasing factor (CRF), novel mammalian CRF related peptides, urocortin 1, urocortin 2, and urocortin 3 have recently been discovered.[2] These CRF ligands display distinct affinity to the two cloned G protein coupled CRF 1 (CRF_1) and 2 (CRF_2) receptors.[1–3] CRF has higher affinity for CRF_1 than for CRF_2 receptor, urocortin 1 displays equal affinity for both subtypes, and urocortin 2 and 3 have selective affinity for CRF_2 receptor.[2 3] In addition to the mapping of CRF ligands and receptors in the brain[2 4] and gut,[5–7] the development of potent selective CRF_1 and CRF_2 antagonists[8 9] and generation of transgenic mouse models[1] provided tremendous insight in the investigation of the underlying mechanisms of stress. Convergent studies established the role of the brain CRF-CRF_1 pathways in mediating the endocrine, autonomic, behavioural, and visceral responses to stress[1 3 10 11] while CRF_2 receptors may be important in dampening stress sensitivity.[1]

Extensive preclinical research effort has solidified the concept that overactivity in the brain CRF-CRF_1 signalling system contributes to the onset of anxiety disorders and depression.[12] These observations have spurred the development of a number of non-peptide CRF_1 receptor antagonists which can readily cross the blood-brain barrier on peripheral administration.[8 9] These compounds prevent various stress related anxiogenic behaviours in rodents.[1 13] Clinical studies in patients with major depression and post-traumatic disorders showed that CRF levels are elevated in the cerebrospinal fluid and lowered by effective antidepressants.[12] In patients treated with interferon α for chronic hepatitis C, activation of the brain CRF pathways induced by interferon-α[14] is frequently associated with psychiatric side effects that have overlapping features with major depression.[15] In mice, synthetic recombinant type I interferon α induced a depressive-like behaviour that is abolished by pretreatment with the CRF_1 receptor antagonist CP-154,526.[16] A first phase II open label clinical trial including patients with major depressive disorders indicated that the CRF_1 antagonist R121919 was effective in reducing depression and anxiety scores.[17] Such beneficial effects were obtained at doses that neither disrupted normal circadian hypothalamic-pituitary axis hormone production nor hampered adrenal corticotrophic hormone (ACTH) or cortisol responses to CRF stimulation.[17] Collectively, existing preclinical and clinical reports indicate that CRF_1 antagonists may have therapeutic potential in the treatment of affective disorders.[1 12 13]

Available evidence suggests that the CRF_1 receptor may also be an appealing target in the context of functional bowel disorders.[18] Irritable bowel syndrome (IBS) is a common bowel disorder with clinical features that include recurrent abdominal pain or discomfort associated with altered bowel habits in the absence of structural pathology.[19] In studies of hospital outpatients with IBS, it has been reported that symptoms or the chronic course of the illness can be exacerbated by psychosocial stressors.[19 20] A high co-prevalence of IBS with psychiatric disorders, including anxiety and depression, is also well documented.[19 21 22] Other clinical studies showed that psychological factors predicted the occurrence of diarrhoea predominant IBS that develops in certain subgroups of patients that had acute gastroenteritis.[19] The underlying mechanisms of such an association may be explained in the framework of overactivity of the CRF-CRF_1 signalling pathways. Evidence supporting this contention came from initial experimental demonstration of an interrelationship between activation of central CRF_1 receptors and stress related induction of IBS-like symptoms.[18] Administration of CRF and urocortin 1 into the lateral brain ventricle stimulated colonic motor function in rats, mice, and gerbils and increased abdominal pain to colorectal distension in rats.[10 23] Sites of action were located at a specific hypothalamic nucleus (paraventricular nucleus) or pontine area [locus coeruleus (LC), LC/Barrington nucleus][10] that also induced CRF related behaviours symptomatic of anxiety and depression.[1 24] Studies with a number of selective CRF_1 antagonists (CP-154,526, CRA-1000, NBI-35965, or NBI-27914) injected intracerebroventricularly or peripherally blunted stress related anxiogenic behaviour, visceral hyperalgesia, and activation of colonic secretory and motor function in rodents and monkeys.[10 11 23 25] Moreover, female mice with deletion of the CRF_1 receptor gene showed reduced anxiety-like behaviour and colonic motor response to the open field test.[26] The colonic response to central CRF-CRF_1 pathway activation is unrelated to pituitary-adrenal hormone release and is mediated by modulation of the autonomic nervous system, particularly stimulation of sacral parasympathetic activity in rodents.[10] There is also a decrease in vagal outflow to the upper gut and activation of the sympathetic nervous system that contribute to the concomitant inhibition of gastric and small intestinal motility.[10 27] Interestingly, it has been found that colorectal distension activates LC activity through CRF-CRF_1 pathways in rodents.[28 29] The increased discharge rate of neurones in the LC induced by stress of psychological or visceral origin leads to widespread activation of noradrenergic projections to forebrain target sites implicated in arousal and attention.[29] These mechanisms may underlay the reported stress induced altered perceptual thresholds to colorectal balloon distension and hyperreactivity to stress in IBS patients.[30]

In addition to the role of brain CRF-CRF_1 pathways, experimental studies have convincingly established peripheral stimulatory actions of CRF on colonic secretory and motor function and permeability.[31] The peptide, injected peripherally, stimulates colonic motility, transit, secretion of mucus, prostaglandins, and ions, degranulates colonic mucosal mast cells and increases intestinal permeability to ions and macromolecules.[32–34] A direct action of CRF at the enteric nervous system was established by the presence of CRF_1 receptors on colonic myenteric neurones.[5] It was also demonstrated that activation of myenteric neurones, increased colonic motility, and induction of diarrhoea induced

by intraperitoneal injection of CRF were mediated by CRF_1 receptors in rodents.[31–36] The relevance of peripheral CRF receptors in the stress response was established by the use of the peptide CRF antagonist α-helical CRF_{9-41} that has poor brain penetrance. This CRF antagonist injected peripherally inhibited restraint stress induced stimulation of colonic motor function, prevented mucosal mast cell degranulation, and blocked the increased colonic mucin and ionic secretion, and intestinal permeability to macromolecules in rats.[31 33] Similar to animal models, intravenous administration of CRF increased colonic motility and abdominal pain in IBS patients and the response was higher compared with normal subjects.[37] Other studies showed that the preferential CRF_1 agonist ovine CRF lowered the stool threshold and sensation of discomfort to colonic distension in normal subjects.[38] In this issue of *Gut*, Sagami and colleagues[39] have built on this framework and report the dampening influence of intravenous injection of the CRF receptor antagonist α-helical CRF_{9-41} on symptoms triggered by colonic tracking distension and electrical stimulation of the rectal mucosa in IBS diarrhoea predominant patients **[see page 958]**. In this study, the authors show that intravenous injection of α-helical CRF_{9-41}, given to subjects unaware of the timing of antagonist administration, blunts the exaggerated motility response in the sigmoid colon to electrical stimulation in IBS patients compared with normal subjects. They also report that the CRF antagonist reduces significantly abdominal pain and anxiety score without compromising pituitary release of ACTH. Because of the small number of subjects included in the study, this initial clinical investigation warrants replication in a larger group of IBS patients and further assessment using a placebo control group. However, these findings, put in the context of existing preclinical and clinical data, support the testing of new CRF antagonists, particularly more potent CRF_1 antagonists, in IBS and the view that CRF_1 receptors are a promising target for the treatment of IBS.

CRF receptors antagonists may also have value in some forms of gut inflammation. A number of studies in rodents and humans established that CRF, acting through CRF_1 receptors, exerts an autocrine-paracrine proinflammatory action in peripheral tissues undergoing an inflammatory process.[40] CRF, urocortin 1, and CRF_1 receptors have been detected at both the gene and protein levels at sites of inflammation[40] in the rodent and human intestine.[41–43] Peripheral administration of CRF_1 receptor antagonists significantly inhibit the degree of inflammation associated with an acute enterotoxic response, as monitored by the reduction in toxin A induced ileal secretion, epithelial cell damage, mucosal oedema, neutrophil infiltration, and mucosal content of interleukin 1β and tumour necrosis factor α.[43] This points to the potential use of specific CRF_1 receptor antagonists in intestinal inflammatory conditions. In the upper gut, other potential clinical relevance of targeting CRF_1 receptors has been recently reviewed in the context of cyclic vomiting syndrome[27] and postoperative gastric ileus.[44]

In summary, a growing body of experimental evidence has demonstrated that CRF_1 receptor antagonists alleviate the development of anxiety-like behaviour and stress related alterations of gut function and enterotoxin mediated intestinal inflammation. The positive results associated with the use of CRF receptor antagonists in IBS patients reported in the present issue of *Gut* hold promise and warrant testing using selective CRF_1 antagonists.

Gut 2004;**53**:919–921.
doi: 10.1136/gut.2003.036400

Correspondence to: Dr Y Taché, CURE/ Digestive Diseases Research Center, Bldg 115, Room 117, VA Greater Los Angeles Health Care System, 1130 Wilshire Blvd, Los Angeles, CA 90073, USA; yTaché@ucla.edu

REFERENCES

1 **Bale TL**, Vale WW. CRF and CRF receptor: Role in stress responsivity and other behaviors. *Annu Rev Pharmacol Toxicol* 2004;**44**:525–57.
2 **Hauger RL**, Grigoriadis DE, Dallman MF, *et al.* International Union of Pharmacology. XXXVI. Current status of the nomenclature for receptors for corticotropin-releasing factor and their ligands. *Pharmacol Rev* 2003;**55**:21–6.
3 **Grammatopoulos DK**, Chrousos GP. Functional characteristics of CRH receptors and potential clinical applications of CRH-receptor antagonists. *Trends Endocrinol Metab* 2002;**13**:436–44.
4 **Morin SM**, Ling N, Liu XJ, *et al.* Differential distribution of urocortin- and corticotropin-releasing factor-like immunoreactivities in the rat brain. *Neuroscience* 1999;**92**:281–91.
5 **Chatzaki E**, Crowe PD, Wang L, *et al.* CRF receptor type 1 and 2 expression and anatomical distribution in the rat colon. *J Neurochem* (in press).
6 **Muramatsu Y**, Fukushima K, Iino K, *et al.* Urocortin and corticotropin-releasing factor receptor expression in the human colonic mucosa. *Peptides* 2000;**21**:1799–809.
7 **Kawahito Y**, Sano H, Kawata M, *et al.* Local secretion of corticotropin-releasing hormone by enterochromaffin cells in human colon. *Gastroenterology* 1994;**106**:859–65.
8 **Zorrilla EP**, Taché Y, Koob GF. Nibbling at CRF receptor control of feeding and gastrocolonic motility. *Trends Pharmacol Sci* 2003;**24**:421–7.
9 **Heinrichs SC**, De Souza EB, Schulteis G, *et al.* Brain penetrance, receptor occupancy and antistress in vivo efficacy of a small molecule corticotropin releasing factor type I receptor selective antagonist. *Neuropsychopharmacology* 2002;**27**:194–202.
10 **Taché Y**, Martinez V, Million M, *et al.* Stress and the gastrointestinal tract III. Stress-related alterations of gut motor function: role of brain corticotropin-releasing factor receptors, *Am J Physiol* 2001;**280**:G173–7.
11 **Habib KE**, Weld KP, Rice KC, *et al.* Oral administration of a corticotropin-releasing hormone receptor antagonist significantly attenuates behavioral, neuroendocrine, and autonomic responses to stress in primates. *Proc Natl Acad Sci U S A* 2000;**97**:6079–84.
12 **Keck ME**, Holsboer F. Hyperactivity of CRH neuronal circuits as a target for therapeutic interventions in affective disorders. *Peptides* 2001;**22**:835–44.
13 **Kehne J**, De Lombaert S. Non-peptidic CRF1 receptor antagonists for the treatment of anxiety, depression and stress disorders. *Curr Drug Target CNS Neurol Disord* 2002;1:467–93.
14 **Capuron L**, Raison CL, Musselman DL, *et al.* Association of exaggerated HPA axis response to the initial injection of interferon-alpha with development of depression during interferon-alpha therapy. *Am J Psychiatry* 2003;**160**:1342–5.
15 **Malaguarnera M**, Laurino A, Di F, *et al.* Neuropsychiatric effects and type of IFN-alpha in chronic hepatitis c. *J Interferon Cytokine Res* 2001;**21**:273–8.
16 **Yamano M**, Yuki H, Yasuda S, *et al.* Corticotropin-releasing hormone$_1$ receptors mediate consensus interferon-α YM643-induced depression-like behavior in mice. *J Pharmacol Exp Ther* 2000;**292**:181–7.
17 **Zobel AW**, Nickel T, Kunzel HE, *et al.* Effects of the high-affinity corticotropin-releasing hormone receptor 1 antagonist R121919 in major depression: the first 20 patients treated. *J Psychiatr Res* 2000;**34**:171–81.
18 **Taché Y**, Martinez V, Million M, *et al.* Role of corticotropin releasing factor receptor subtype 1 in stress-related functional colonic alterations: implications in irritable bowel syndrome. *Eur J Surg* 2002;**168**(suppl 587):16–22.
19 **Jones J**, Boorman J, Cann P, *et al.* British Society of Gastroenterology guidelines for the management of the irritable bowel syndrome. *Gut* 2000;**47**(suppl 2):ii1–19.
20 **Mönnikes H**, Tebbe JJ, Hildebrandt M, *et al.* Role of stress in functional gastrointestinal disorders. Evidence for stress-induced alterations in gastrointestinal motility and sensitivity. *Dig Dis* 2001;**19**:201–11.
21 **Lydiard RB**. Irritable bowel syndrome, anxiety, and depression: what are the links? *J Clin Psychiatry* 2001;**62**(suppl 8):38–45.
22 **Solmaz M**, Kavuk I, Sayar K. Psychological factors in the irritable bowel syndrome. *Eur J Med Res* 2003;**8**:549–56.
23 **Martinez V**, Wang L, Rivier J, *et al.* Central CRF, urocortins and stress increase colonic transit via CRF1 receptors while activation of CRF2 receptors delays gastric transit in mice. *J Physiol* 2004;**556**:221–34.
24 **Weiss JM**, Stout JC, Aaron MF, *et al.* Depression and anxiety: role of the locus coeruleus and corticotropin-releasing factor. *Brain Res Bull* 1994;**35**:561–72.
25 **Million M**, Grigoriadis DE, Sullivan S, *et al.* A novel water-soluble selective CRF_1 receptor antagonist, NBI 35965, blunts stress-induced visceral hyperalgesia and colonic motor function in rats. *Brain Res* 2003;**985**:32–42.
26 **Bale TL**, Picetti R, Contarino A, *et al.* Mice deficient for both corticotropin-releasing factor receptor 1 (CRFR1) and CRFR2 have an impaired stress response and display sexually dichotomous anxiety-like behavior. *J Neurosci* 2002;**22**:193–9.
27 **Taché Y**. Cyclic vomiting syndrome: the corticotropin-releasing-factor hypothesis. *Dig Dis Sci* 1999;**44**:79–86S.
28 **Lechner SM**, Curtis aL, Brons R, et al. Locus coeruleus activation by colon distention: role of corticotropin-releasing factor and excitatory amino acids. *Brain Res* 1997;**756**:114–24.
29 **Lejeune F**, Millan MJ. The CRF1 receptor antagonist, DMP695, abolishes activation of locus coeruleus noradrenergic neurones by CRF in anesthetized rats. *Eur J Pharmacol* 2003;**464**:127–33.
30 **Dickhaus B**, Mayer EA, Firooz N, *et al.* Irritable bowel syndrome patients show enhanced modulation of visceral perception by auditory stress. *Am J Gastroenterol* 2003;**98**:135–43.